C1

1. In a cell population comprising dividing and quiescent cells, wherein said dividing cells comprise cancer and endothelial cells, a method for substantially and selectively killing said dividing cells, said method comprising contacting said cell population under infective conditions with a replication competent adenovirus comprising a mutation in the E1A RB family member binding region of said adenovirus, and allowing sufficient time for said adenovirus to infect said cell population.

C2

6. A method as described in claim 5 wherein said mutation in the E1A-CR2 region is in Ad5 and comprises a deletion or substitution of one or more amino acids 122 through 129 encoded by said E1A-CR2 region.

REMARKS

General

The Examiner has requested new drawings, and the Applicants will submit them at such time that there is an indication of allowable subject matter.

As requested by the Examiner, a clean copy of all pending claims is provided herewith as Appendix B. Appendix A presents the amended claims.

Rejections

35 U.S.C. §112, First and Second Paragraphs

Claims 1-24 stand rejected under §112, first paragraph, because the Examiner believes that the Specification "...while being enabling for methods of substantially and selectively reducing tumor size by the intratumoral injection of Ad5 adenoviral vectors dl922/947 or dl1107 or pm 928, does not reasonably provide enablement for other limitations encompassed by the claims." Applicants will first address the issue of mode of administering the subject adenoviral vectors. Applicants understand that while they have

shown a limited number of modes of administration, they beg to differ with the Examiner that their claims are not enabled for other modes of administration, aside from intratumoral injection, and offer the following reasons.

On page 7, lines 21-22 the Examiner will note that the Applicants contemplated modes of administration other than intratumoral. For example, there Applicants state that "Standard techniques are used...pharmaceutical formulation and delivery, and treatment of patients." Clearly, a skilled practitioner of this art would understand that Applicants intend that standard modes of administering adenovirus include systemic administration which could be achieved by a number of means, including intravenous injection.

Moreover, the Examiner will further note that Applicants have incorporated by reference U. S. Patent No. 5, 6,77, 178 in its entireity. Column 17, lines 1-20, states:

> A adenovirus suspension containing about 10.sup.3 to 10.sup.12 or more virion particles per ml may be inhaled as a mist (e.g., for pulmonary delivery to treat bronchogenic carcinoma, small-cell lung carcinoma, non-small cell lung carcinoma, lung adenocarcinoma, or laryngeal cancer) or swabbed directly on a tumor site for treating a tumor (e.g., bronchogenic carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma, cervical carcinoma) or may be administered by infusion (e.g., into the peritoneal cavity for treating ovarian cancer, into the portal vein for treating hepatocarcinoma or liver metastases from other non-hepatic primary tumors) or other suitable route, including direct injection into a tumor mass (e.g., a breast tumor), enema (e.g., colon cancer), or catheter (e.g., bladdercancer).

Incorporation of this patent, with the relevant section presented above, clearly supports other modes of administering adenovirus in addition to intratumoral rejection.

Lastly, Applicants point the Examiner to page 19, lines 21-22, where Applicants state that "Cotton rats were given intranasal inoculations of either

dl922/947 or wild-type adenovirus...." Thus, that Applicants used "intranasal inoculations" provides further support that Applicants' claims are enabled for administering the invention viruses by other than direct injection.

Finally, and in further regard to the §112 rejection concerning the enablement of Applicants' in vivo results, Applicants respectfully direct the Examiner's attention to Examples 3 and 4 of their Specification, and to their past amendments regarding this issue. In the Examples, and elsewhere in the Specification, Applicants' have enabled the claimed in vivo applications of the instant invention viruses by showing that these viruses kill dividing cells, cancer and endothelial cells, but not quiescent normal cells. Previously, the Examiner has questioned these results, primarily because Applicants' data were generated from both in vivo and in vitro experiments. The Examiner is requiring that all of Applicants' data be from in vivo model systems. In this regard, Applicants draw the Examiner's attention to the standard for enablement set forth in In re Marzocchi et al., (CCPA 1971) 439 F2d, 169 USPQ 367. There the court held that §112, First Paragraph, requires nothing more than objective enablement. Applicants believe that their disclosure satisfies this standard considering the level of detail in the Specification, and the ease with which the invention can be practiced.

Briefly, and by way of review, Applicants refer the Examiner to Example 3, on page 18 of the Specification, wherein Applicants describe, in some detail, an in vivo experiment which shows the selective killing of dividing cells (tumor cells) that have been injected with an E1A-CR2 Rb binding site mutant adenovirus. Further, Example 4

goes beyond the results shown in Applicants' Example 3, in that it shows data from a cotton rat, which is permissive for adenoviral replication, that the E1A-CR2 Rb binding site viruses have limited, or no, killing capacity for quiescent normal cells.

Thus, the results in Examples 3 and 4, *which present in vivo results,* clearly show that Applicants' methods are enabled for the claimed in vivo applications of the instant E1A-CR2 Rb mutant viruses. Most importantly, these viruses show selective in vivo killing in the sense that they will kill dividing cells, cancer cells, but not quiescent normal cells.

What the Examiner is relying on to maintain the rejection is the in vitro experiment shown in Example 2, page 17 of the specification. There Applicants show that the E1A-CR2 Rb binding site mutants replicate in, and kill, actively proliferating micro-vascular endothelial cells. The Examiner is requiring that these results be from an in vivo animal model system. Applicants disagree.

Applicants respectfully submit that a reasonably skilled practitioner of this art would easily embrace Applicants' in vitro data to be predictive of the in vivo setting since in vitro model systems are routinely used in the field of oncolytic viruses to predict the in vivo killing properties of adenoviruses. The Examiner is referred to U.S. Patent No. 5,998,205 (Generic Therapeutics, Inc.) and U.S. Patent No. 5,698,443 (Calydon, Inc.). There are also many scientific publications that describe oncolytic adenoviruses and their killing properties. Two are: Journal of Virology, July 2000, page 6147, titled "Tumor-Specific Replication-Competent Adenovirus Vectors Overexpressing the Adenovirus Death Protein," and the Journal of Virology, March 2001, page 2857, titled "Replicating

Adenoviruses that Target Tumors with Constituative Activation of the WNT Signaling Pathway."

Applicants respectfully submit that all the above arguments, taken individually or collectively, should obviate the lack of enablement rejection.

Claims 6 and 7 stand rejected under §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner has stated that claims 6 and 7 are not limited to Ad5. The Examiner will note that these claims have been amended to refer to Ad5, and thus reference to the specific CR2 regions of the virus is no longer indefininte.

The Examiner has further stated that since E1A encodes 3 polypeptides, claims 6 and 7 are indefinite because they don't recite which polypeptides are mutated. Applicants believe that a skilled practitioner of this art would know what Applicants intend by referring to the definition section of Applicants' Specification which states that:

> By "E1A RB family member binding regions", "RB binding site mutants" or "RB mutants" in adenovirus is meant those regions in the conserved region 2 (CR2) of E1A responsible for binding RB (p105), or two other E1A binding proteins, p107, and p130. Figure 1 shows the specific CR2 gene deletions present in the adenoviral mutants dl922/947, dl1107, and the point mutation in pm928.

The Examiner has also stated that claims 6 and 7 are indefinite as they recite mutations in the E1A-CR2 region, which are composed of amino acids, and has requested that the claims be amended to clarify that this region encodes the relevant amino acids. Applicants have made the amendment, as requested.

Thus, Applicants believe that claims 6 and 7, as amended, are not indefinite and respectfully request that the rejection be withdrawn.

35 U.S.C. §102(b) Rejections

Claims 21 and 22 stand rejected under §102(b) as being anticipated by Yamashita, T. et al., (Oncogene (1993), 8, 2433-2441), and claims 21, 23 and 24 stand rejected under 102(b) as being anticipated by Shisler, J, et al. (Journal of Virology, Jan. 1996, page 68-77).. Applicants respectfully submit that neither Yasmashita, T., et al., nor Shisler, J., et al., show Applicants' claimed "pharmaceutical composition" which consist of a "physiological solution." Rather, what is shown is the virus, dl922/947, or other E1A mutants, respectively, in a solution containing fetal bovine serum. This, of course, is not a component of a "pharmaeutical composition" for use in administering Applicants' invention viruses to humans. Thus, Applicants submit that claims 21 and 22, and 21, 23, and 24 are not anticipated by Yamashita, et al, nor by Shisler, J., et al., respectively.

35 U.S.C. §102(e)

Claims 1-6, 21 and 25 stand rejected under §102(e) as being anticipated by Bishoff et al., (U.S. 6, 080, 578). The Examiner will note that claim 1, and claims 2-6 by their dependency on claim 1, has been amended to recite that the "dividing cells" consist of "cancer cells and endothelial cells." Nowhere in the cited reference of Bishoff et al., is there a showing that the viruses described there have the killing activity ascribed to the adenoviruses claimed in the instant claims. Thus, since a reference must show each and every feature of what an applicant claims to support a §102(e) rejection, and this is not the case here, Applicants respectfully request that the rejection be withdrawn.

The Examiner has also rejected claims 21 and 25 based on Bsihchoff et al. These claims have been cancelled.

35 U.S.C. §103 Rejections

Claims 1-10, 21-28 stand rejected under §103(a) as being unpatentable over Bischoff et al. (U.S. Patent No. 6,080,578) in view of Yamashita, T. et al., or Shisler, J. et al.

Applicants note that as amended, claims 1-10 cannot be considered obvious based on the primary reference, Bischoff et al., for the reason that, as amended, claim 1 recites:

> "In a cell population comprising dividing and quiescent cells, wherein said *dividing cells comprise cancer and endothelial cells*, a method for substantially and *selectively killing said dividing cells*, ..."

There is neither a showing nor suggestion in Bischoff et al., that the invention adenoviruses could be used to realize this effect. That is, that the adenoviruses can kill two types of dividing cells; cancer cells and endothelial cells. Applicants also note that the secondary references similarly do not, even remotely, show or suggest what Applicants have claimed in claims 1-10.

Regarding claims 21-28, the rejection is moot as to claims 21 and 25 as these claims have been cancelled.

Further, as for claims 22, 23, and 24, since Bischoff et al., do not teach Applicants' adenoviruses, dl922/947, dl1107, and pm928, and neither Yamashita, T. et al., nor Shisler, J. et al., show or suggest a "pharmaceutical composition" it is respectfully not seen that these references can properly support a §103 rejection. Recall, that the use

of fetal bovine serum by these inventors in their solutions eliminates them from being a "pharmaceutical composition."

Finally, regarding claims 26, 27, and 28 since Bischoff et al., do not show Applicants' adenoviruses, dl922/947, dl1107, and pm928, and neither Yamashita, T. et al., nor Shisler, J. et al., show or suggest a "composition" of such adenoviruses "with a negative selection agent operably linked to a promoter," Applicants believe that these claims are also unobvious.

Based on the discussion above, Applicants respectfully submit that claims 22-24, and claims 26-28 are not obvious, and request that the §103 rejection be withdrawn.

Applicants believe that the instant patent application is in condition for allowance, and ernestly solicits the Examiner to expedite examination. If the Examiner has any questions of a general or specific nature, the Examiner is encouraged to telephone the undersigned.

Extension of Time Pursuant to 37 C.F.R. §1.136(a)

Applicant respectfully requests a 3-month extension of time to file a Response to the Final Office Action mailed January 17, 2002. The extended period expires on June 17, 2002. Please charge the 3-month extension fee to Deposit Account No. 15-0615.

The Commissioner is authorized to charge any fees for a large entity associated with this response to Deposit Account No. 15-0615 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: 7/17/02

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